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(54) High dosage topical forms of collagenase.

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European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 92 31 0008

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 5)
X Y	US-A-3 792 161 (FOX C.L.) * abstract * * column 1, line 69 - column 2, line 15 * ---	1-3 1-5,8-10	A61K37/54 A61K9/14 A61K47/36 A61L15/38
X Y	US-A-4 524 065 (S.R.PINNELL) * column 2, paragraph 1 * * column 1, line 59 - column 2, line 8 * ---	1-2 1-5,8-10	
Y	GB-A-2 150 833 (CESKOSLOVENSKA AKADEMIE VED) * abstract; claims 1-2 * ---	1-5,8-10	
Y	CH-A-437 641 (VEB SERUM-WERK BERNBURG) * the whole document * ---	1-5,8-10	
A	EP-A-0 312 208 (ETHICON INC.) * claims * -----	1-10	

TECHNICAL FIELDS SEARCHED (Int. Cl. 5)

A61K

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims

Claims searched completely: 1-14,19-20

Claims searched incompletely:

Claims not searched: 15-18

Reason for the limitation of the search:

method for treatment of the human or animal body by therapy (article 52 (4) EPC)

Place of search	Date of completion of the search	Examiner
BERLIN	23 APRIL 1993	AVEDIKIAN P.F.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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(54) High dosage topical forms of collagenase.

(57) This invention provides pharmaceutical compositions for topical application containing high concentrations of the enzyme collagenase in non-aqueous excipients. The invention also provides a particular excipient, dextran, which is especially useful for admixture with collagenase and which can also be used to advantage with uother pharmaceutically active materials.

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Collagenase ointment has been available in the United States as Collagenase Santyl(R) Ointment (Advance Biofactures Corp., Lynbrook, NY 11563) for 27 years. It has been used on millions of patients. The concentration of collagenase in Santyl(R) Ointment has been no greater than 300 ABC units per gram of ointment. Collagenase ointment has also been available in other countries. It is useful for the debridement of burns and of dermal ulcers, particularly bed sores (decubitus ulcers). The debridement of these lesions is necessary to remove dead and dying tissue that is typically a source of microbial infection. In addition, healing does not take place until this necrotic material is removed. Speedof debridement is thus a therapeutic desideratum.

Collagenase ointment has not been so widely accepted by the burn centers in the treatment of third degree burns as perhaps its efficacy deserves. This lack of acceptance is largely due to the perception that third degree burns in particular require a more rapid debridement than the collagenase ointment can provide. A more rapid debridement of severe burns without the necessity for anesthesia or a surgical operation would constitute a therapeutic advancement.

A more rapid debridement would also be useful in the treatment of dermal ulcers since it would provide a superior cost/benefit profile.

Dextrans are polysaccharides produced by certain bacteria (e.g. Leuconostoc mesenteroides) and consist of chains of α-D-glucopyranosyl residues linked predominantly by α-(1→6)-linkages, with a small-fraction of α(1→3)-linkages which give rise to chain branching. Dextrans are available in various molecular-weight fractions. Dextran fractions with weight average molecular weights of 40,000, 70,000 and 75,000 daltons have found therapeutic uses as plasma volume expanders. The 40,000-dalton fraction is also used as a blood flow adjuvant. [ref. Merck Index, Tenth Edition, #2911] In addition, dextran is used in lubricant eye drops and hysteroscopy fluids. [ref. PDR, 45th edition, 1991]

Dextrans are commercially available as a fine white powder that is approved for pharmacological use. The powder absorbs water readily and hence is useful as a drying agent for wounds, and is completely soluble in sufficient amounts of water.

Pharmacologically active ingredients such as enzymes, antibiotics, antifungals, anti-inflammatories, antipyritics, etc are usually diluted with an excipient for topical use as creams, ointments, lotions, solutions, etc. Many such excipients decrease the shelf life of drug substances.

SUMMARY OF THE INVENTION

In accordance with one aspect of this invention, a pharmaceutical composition is prepared by intimately admixing a dry powdered drug substance suited for topical application, with dry powdered dextran. By drug substance or pharmaceutical is meant a material that is pharmaceutically active or that becomes active upon admixture with water.

A preferred embodiment is a dry powdered intimate admixture of dextran and collagenase. The enzyme collagenase is derived from fermentation by Clostridium histolyticum, and is purified by a chromatographic technique. It possesses the unique ability to digest native and denatured collagen in necrotic tissue. Advantageously, one gram of the admixture contains from 500 to 5,000 ABC units of collagenase; and, as will be explained below, an especially advantageous mixture contains in excess of 2,500 up to 10,000 or more ABC units of collagenase per gram of dextran. It is useful for debridement of burns and of decubitus ulcers, generally known as bed sores. The mixture can be shaken or sprayed onto the burn or ulcer, and a homogeneous mixture of the dextran and collagenase will thus reach the affected site. The fluids available from the wound will dissolve the dextran and make the active enzyme available where it is needed.

This invention further provides pharmaceutical compositions wherein dextran or other non-aqueous excipient is mixed with the enzyme collagenase at a collagenase concentration much greater than has heretofore been used in practice, and higher than heretofore mentioned in the literature to our knowledge. These compositions, when used topically to treat burns, ulcers and other wounds, provide rapid debridement of dead and dying tissue without causing undesirable side effects.

The pharmaceutical compositions of this aspect of the invention contain at least about 1,500 ABC units collagenase per gram of excipient, and preferably range from greater than 2,500 up to 10,000 or more units per gram of excipient. For many applications the concentration will exceed 5,000 units/gram of excipient, e.g., 8,000 units/gram of excipient. In general, within these ranges one should use higher concentrations in powdered or liquid compositions than in ointments, because more of the latter can be applied to and maintained on the area to be treated. Preferred ranges for ointments are about 1,500 to about 5,000 and for powders or liquids are about 2,500 to about 10,000 ABC units collagenase per gram of excipient.

These pharmaceutical compositions are prepared by intimately admixing a sterilized col-

lagenase powder with a non-aqueous solid or liquid excipient. Excipients that can be used include (but are not limited to) dextran, white petrolatum USP, isopropyl myristate NF, and lactose NF. In addition, an antibiotic or antiseptic powder such as Polysporin(R) antibiotic, gentamicin, and/or silver sulfadiazine may be added, or may constitute the excipient itself.

By non-aqueous excipient is meant a liquid or solid material that is inert towards, i.e., does not significantly affect adversely the physiological activity of, the collagenase, and that is substantially free from water. Water is an undesired constituent. The water or other aqueous solutions of collagenase taught in the literature, if prepared in advance for use, would generally have a safe shelf life at room temperature of not over two weeks.

DETAILED DESCRIPTION

The potency assay of collagenase is based on the digestion of undenatured collagen (from bovine tendon) at pH 7.2 and 37° C for 20-24 hours. The number of peptide bonds cleaved are measured by reaction with ninhydrin. Amino groups released by a trypsin digestion control are subtracted. One net ABC unit of collagenase will solubilize ninhydrin reactive material equivalent to 1.09 nanomoles of leucine per minute.

Sterilized collagenase powder is available having a minimum assay of 50 ABC units per mg. The assay may range considerably above that from batch to batch, but is taken into account in determining the weight of powder to admix with excipient to give the desired number of collagenase units per gram of excipient.

Dextrans are useful for the delivery of desired amounts of medication to topical wounds, burns, infections, inflammations, lacerations, ulcers. Included in such medications are collagenase and other enzymes, antibiotics, anesthetics, antifungals, anti-inflammatory agents (steroidal and non-steroidal).

Since the affected area is not touched, the application of the dry powdered mixture of dextran and medication can be less painful than would be the case if the medication were applied as a cream, gel, lotion, ointment, etc. In addition, no cream, gel, lotion, or ointment needs to be removed between dressings: the dextran formulation is soluble, only gentle lavage with an appropriate liquid, such as normal saline, is needed to cleanse the area.

Dry powdered dextrans provide the following further advantages for use in admixture with dry powdered pharmaceuticals:

1. They readily dissolve in the fluids available at a wound site.
2. Their dissolution provides an in situ release of the active ingredient.
3. All of the active ingredient is available at the wound site, as opposed to an ointment, wherein some of the active ingredient may remain trapped in the ointment matrix.

There are also economic advantages to using dextrans as described herein since the mixing and filling of dry ingredients is less costly than the mixing of ointments, creams, and lotions and their filling into tubes and/or glass jars.

Thus dextrans of various molecular weights, fine dry powders that have no intrinsic therapeutic activity and that are well tolerated by man and animals, can safely and advantageously be used as carriers for dry pharmaceuticals when used topically.

Whether application is made by dusting or spraying, a homogeneous dry powdered mixture of the dextran and active ingredient will reach the affected site, and the aqueous fluids available from the wound will dissolve the dextran and make the active ingredient available where it is needed.

Dry powdered intimate admixtures of dextran and one or more topical pharmaceuticals include, by way of example, the following (the percentages are by weight).

A. Dextran with ½ - 20% collagenase as a debriding agent.

B. Dextran with other enzymes recognized for their therapeutic activity when used topically.

C. Dextran with 0.1% Gentamicin as an antibiotic.

D. Dextran with other antibiotics; e.g., neosporin, silver sulfadiazine, chloramphenicol, and other antibiotics deemed safe and effective when used topically.

E. Dextran with ½ - 20% benzocaine as an anesthetic.

F. Dextran with other topical anesthetics, whether natural or synthetic; e.g. lidocaine, etc.

G. Dextran with 1% clotrimazole as an antifungal agent.

H. Dextran with other topical antifungal agents, e.g. nystatin, ketoconazole.

I. Dextran with 0.01 - 2½% hydrocortisone as an anti-inflammatory agent.

J. Dextran with other steroidal or nonsteroidal anti-inflammatory drugs, e.g., halcinonide, triamcinolone acetonide, that can be used topically.

K. Dextran with other therapeutic agents that are deemed safe and effective when used topically.

While ranges of weight per cent are given, one skilled in the pharmaceutical arts will make the choice based on activity of the drug and appropriate concentrations for the intended use. More than one concentration of a particular drug may be

made available to the physician. In general, for most pharmaceuticals, the concentration will be within the broad range of about 0.01 to 30 weight percent pharmaceutical in the mixture.

Dextrans used will ordinarily be in the range of about 20,000 to 100,000 daltons molecular weight. The intended use may affect the choice, the higher molecular weights giving a more viscous drug-containing liquid when the powder absorbs exudate from the wound.

Dextrans and most other dry excipients are available commercially as fine dry powders, as are purified collagenase and most other pharmaceuticals. The mixing of dry powders is within the skill of the art, and various kinds of apparatus can be obtained from commercial suppliers. Taking dextran as an example, it is best to mix and package in a controlled atmosphere of low or zero humidity. For many drugs subject to easy oxidation, an inert atmosphere, e.g. nitrogen or helium, can be used.

Rather than mixing dry powders, it is possible to dissolve dextran or other soluble excipient and the desired pharmaceutical(s) in a solvent, usually water with or without another water soluble solvent such as a lower alcohol, and either precipitate the solutes as by chilling or adding a non-solvent followed by drying, or spray-dry the solution, or lyophilize the solution, to obtain the dry powdered mixture of pharmaceutical and excipient. Drying of a precipitate followed by grinding, if necessary, should be carried out at near room temperature or lower in a selected atmosphere as described above; likewise spray-drying, which can also advantageously be conducted in vacuo. All such operations are within the skill of the art.

The particle size of final product is not critical, so long as it dusts or flows easily.

Since dextrans and a number of other powdered excipients absorb moisture easily, and many drug substances are adversely affected by water, our dry powder pharmaceutical compositions should be packaged so as to prevent moisture from entering: therefore, the material from which the package is constructed should be a vapor barrier, and replaceable closures should insure a tight seal.

Packages may take on a number of forms, selected and designed for different needs:

1. Shaker containers, whereby the mixture can be dusted over open surface areas.
2. Aerosol containers (atomizers), whereby the mixture can be sprayed onto or into an affected area by gentle gas or air pulses.
3. Single unit envelopes, which may contain, say, from ½ to 30 grams of the mixture as a single unit dose. Shaker and/or aerosol containers can be fitted with volume controls so that a predetermined quantity (single unit dose) of the powdered mixture is released.

The preparation of ointments by various procedures is within the skill of the art, and various kinds of apparatus can be obtained from commercial suppliers. The high-dosage collagenase ointments of this invention can be packaged in glass jars, squeezable tubes, or in sealed single unit dose envelopes.

The admixture of finely divided solids with liquids is likewise within the skill of the art, as by using high-speed bladed stirrers or other commercially available apparatus. Liquid compositions of this invention can be packaged in bottles, jars, single unit dose envelopes, or preferably aerosol containers which should be well shaken before use to spray onto or into the area to be treated.

It may be desirable to include in our pharmaceutical compositions one or more other medicaments. Often an antibiotic or antiseptic is added for general prophylaxis against infection and/or to fight infection already present. Other useful additions are anti-inflammatory agents and local anesthetics or analgesics.

For the convenience of the physician, nurse, or other user, a pharmaceutical kit may be sold containing a shaker, spray can, tube or other package containing a pharmaceutical composition of this invention together with a separate shaker or spray can or other package containing an antibiotic in any conventional form. Rather than or in addition to the antibiotic, one can use in a separate package in the kit any medicament intended to reduce infection or to alleviate pain or to induce general healing.

With respect to our high-dosage collagenase compositions, in addition to the non-aqueous excipients mentioned above, further examples of those that may be used are powdered cornstarch, talc. A further example of ointment base is lanolin (caution: allergenic to a small percentage of the population). Suitable liquid excipients are mineral oil, glycerol. Any material proposed for use as an excipient must first be tested in the intended formulation to determine that it is indeed substantially inert towards the collagenase over a considerable length of time, i.e., the desired assured shelf life.

DRAWINGS

Chart 1 shows percentage debridement as a function of time, as determined in Experiment Number 1 below, using two different concentrations of collagenase in Polysporin(R), one ten times greater than the other.

Chart 2 shows percentage debridement as a function of time, as determined in Experiment Number 2 below, using two different concentrations of collagenase in petrolatum, one ten times greater than the other.

Chart 3 shows percentage debridement as a function of time, as determined in Experiment Number 3 below, using two different concentrations of collagenase in lactose NF, one five times greater than the other.

EXAMPLES OF HIGH-DOSAGE COLLAGENASE

Sterile collagenase powder is available from Advance Biofactures Corporation of Lynbrook, NY 11563.

White petrolatum USP is commercially available from Witco Chemical.

Polysporin(R) is commercially available from Burroughs Wellcome.

Lactose NF is commercially available from a number of sources, e.g., DMV Campina, Inc.

A number of experiments were carried out to compare the debriding effect of a high-dosage pharmaceutical preparation with a normal dose preparation. In each experiment a number of guinea pigs were anesthetized and were given bilateral third degree burns by being scalded for 20 seconds with a 100-ml beaker containing boiling water. This method produces a well-defined burn and burn eschar of a reproducible size. Some of the burns were treated with the standard amount of collagenase. The other burns were treated with up to ten times the standard amount. All burns were treated with antibiotic. The percentage debridement was assessed by visual inspection and by serial photographic evidence.

The following examples illustrate the difference between standard dose preparations and high-dosage preparations.

Experiment Number 1: Eight guinea pigs were given bilateral third degree burns. Seven of the burns were controls and were treated daily by sprinkling approximately 1 g of Polysporin(R) which contained 800 ABC units of collagenase powder. the lesion was then covered with a 3x3-in sterile gauze pad containing a thin layer of sterile petrolatum. This procedure was repeated for 4 days. The test sides were treated in an identical manner, except that each gram of Polysporin(R) contained 8,000 ABC units of collagenase powder. (The presence of a Polysporin(R)-resistant Proteus mirabilis infection necessitated the use of gentamicin powder, which was sprinkled on the wound after treatment with collagenase/Polysporin(R) but before covering with the gauze pad. Sides 61L, 61R, 62L, 62R, 63L, 63R, 64L, and 64R were treated with gentamicin on the second, third, and fourth days subsequent to burning.)

The results of this experiment are presented in Table 1 and Chart 1. Note that the average percentage debridement with 8,000 ABC units is significantly better (at the 99% degree of confidence, based on the Wilcoxon test) than the debridement seen with 800 ABC units for all four days.

Experiment Number 2: Eight guinea pigs were given bilateral third degree burns. Half of the burns were controls and were treated daily by applying a sterile gauze pad containing about 3 g of an ointment of white petrolatum USP containing 270 ABC units of collagenase per gram of petrolatum. This procedure was repeated for 4 days. The test sides were treated in an identical manner, except that the petrolatum used contained 2,700 ABC units of collagenase powder per gram of petrolatum. Gentamicin powder was sprinkled onto the burns of animals 80, 81, 82, and 83 before the collagenase/petrolatum ointment was applied. Similarly, silver sulfadiazine powder was used on animals 86, 87, 88, and 89.

The results of this experiment are presented in Table 2 and Chart 2. Note again that the high-dosage treatment debrided significantly faster than the standard-dose treatment.

Experiment Number 3: Seven guinea pigs were given bilateral third degree burns. Half of the burns were controls and were treated daily by sprinkling on the wound silver sulfadiazine followed by approximately 1 g of lactose NF that contained 800 ABC units of collagenase powder. The burn was then covered with a 3x3-in sterile gauze pad containing a thin layer of sterile petrolatum. This procedure was repeated for 4 days. The test sides were treated in an identical manner, except that each gram of lactose NF contained 4,000 ABC units of collagenase powder.

The results of this experiment are presented in Table 3 and Chart 3. Note again that the high-dosage treatment debrided significantly faster than the standard dose treatment.

EXAMPLES WITH DEXTRAN

Comparisons were made of the rate of debridement of burns when treated with dextran/collagenase combinations and with collagenase-containing ointment (Santyl(R) Ointment; contains 250 ABC units of collagenase per gram of white petrolatum USP; manufactured by Advance Biofactures Corp. of Lynbrook, NY 11563).

Four burn experiments, comprising a total of eighteen guinea pigs, were carried out to compare the debriding effect of dextran/collagenase combinations to that of Santyl(R) Ointment. An antibiotic was used in all cases. Thirteen sides were each treated with 3 grams of Santyl(R) Ointment. Seven sides were treated with a dextran/collagenase mixture. Sterile gauze pads with a thin layer of sterile petrolatum to avoid sticking were used on all surfaces containing the dextran/collagenase ap-

plicacation. 0.5 gm of the dextran/collagenase combination is one application on a burn surface.

Experiment Number I: Neosporin powder was used as the antibiotic in conjunction with Santyl(R) Ointment. The powder was first sprinkled on the surface of the wound. Gentamycin cream was used as the antibiotic in conjunction with dextran containing 750 ABC units of collagenase powder per gram of dextran. The dextran/collagenase combination showed faster debridement in the first 48 hours of the experiment. By the fourth day, all sides showed equal percentage debridement. The edge of the burn area was more completely debrided when using the dextran/collagenase powder combination.

Experiment Number II: Santyl(R) Ointment containing 0.1% Gentamycin sulfate powder was compared to dextran/collagenase/Gentamycin sulfate powder at 750 ABC units/g and 375 ABC units/g concentrations of collagenase powder in the dextran. The powder contained 0.1% Gentamycin sulfate. The dextran/collagenase/Gentamycin powder with 750 ABC units/g concentration of collagenase showed faster debridement than the other two test preparations in the first 48 hours. By the fourth day, all sides showed equal percentage debridement. The edge of the burn area was more completely debrided when using the dextran/collagenase combinations.

Experiment Number III. This was the same as Experiment Number II, except that an additional two animal sides were treated with a dextran/collagenase/Gentamycin combination containing 1500 ABC units/g concentration of collagenase. The results showed that the dextran/collagenase combination using all three different concentrations of collagenase exhibited faster debridement in the first 48 hours, with the 1500 ABC units/g concentration being the fastest compared to Santyl(R) Ointment.

Experiment Number IV. The debriding effect of Santyl(R) Ointment was compared to that of a dextran/collagenase combination with 1500 ABC units of collagenase powder per gram of dextran. The antibiotic used was silver sulfadiazine powder sprinkled onto the wound surface before the application of the treatment. At the end of the experiment (4 days), the dextran/collagenase treated side had a greater percentage of debridement than the Santyl(R) Ointment treated side.

Claims

1. A pharmaceutical composition for topical use comprising an intimate admixture of a non-aqueous excipient and at least about 1,500 ABC units of collagenase per gram of excipient.

2. A composition according to claim 1 in the form of an ointment.

3. A composition according to claim 2 wherein the excipient is petrolatum.

4. A composition according to either of claims 2 or 3 containing from about 1,500 to about 5,000 ABC units of collagenase per gram of excipient.

5. A composition according to claim 1 wherein the excipient is a dry powder.

6. A composition according to claim 5 wherein the excipient is lactose.

7. A composition according to claim 5 wherein the excipient is Polysporin(R).

8. A composition according to claim 5 wherein the excipient is dextran.

9. A composition according to any of claims 5-8 containing from about 2,500 to about 10,000 ABC units of collagenase per gram of excipient.

10. A pharmaceutical composition comprising a dry powdered intimate admixture of dextran and collagenase.

11. A pharmaceutical composition comprising a dry powdered intimate admixture of dextran and a pharmaceutical suited for topical application.

12. A composition according to claim 11 wherein said pharmaceutical is an enzyme.

13. A composition according to claim 11 wherein said pharmaceutical is an antibiotic.

14. A composition according to claim 11 containing from about 0.01 to 30 weight percent pharmaceutical.

15. A method of treating a wound or other condition of the body treatable topically which comprises applying thereto a composition according to any of claims 1-9.

16. A method according to claim 15 wherein the condition is a burn.

17. A method according to claim 15 wherein the condition is a decubitus ulcer.

18. A method of treating a wound or other condition of the body treatable topically which comprises applying thereto a composition according to any of claims 10 - 14.

19. A dispensing container containing a pharmaceutical composition according to any of claims 1 - 14.

20. A container according to claim 19 that dispenses a single unit dose of the composition.

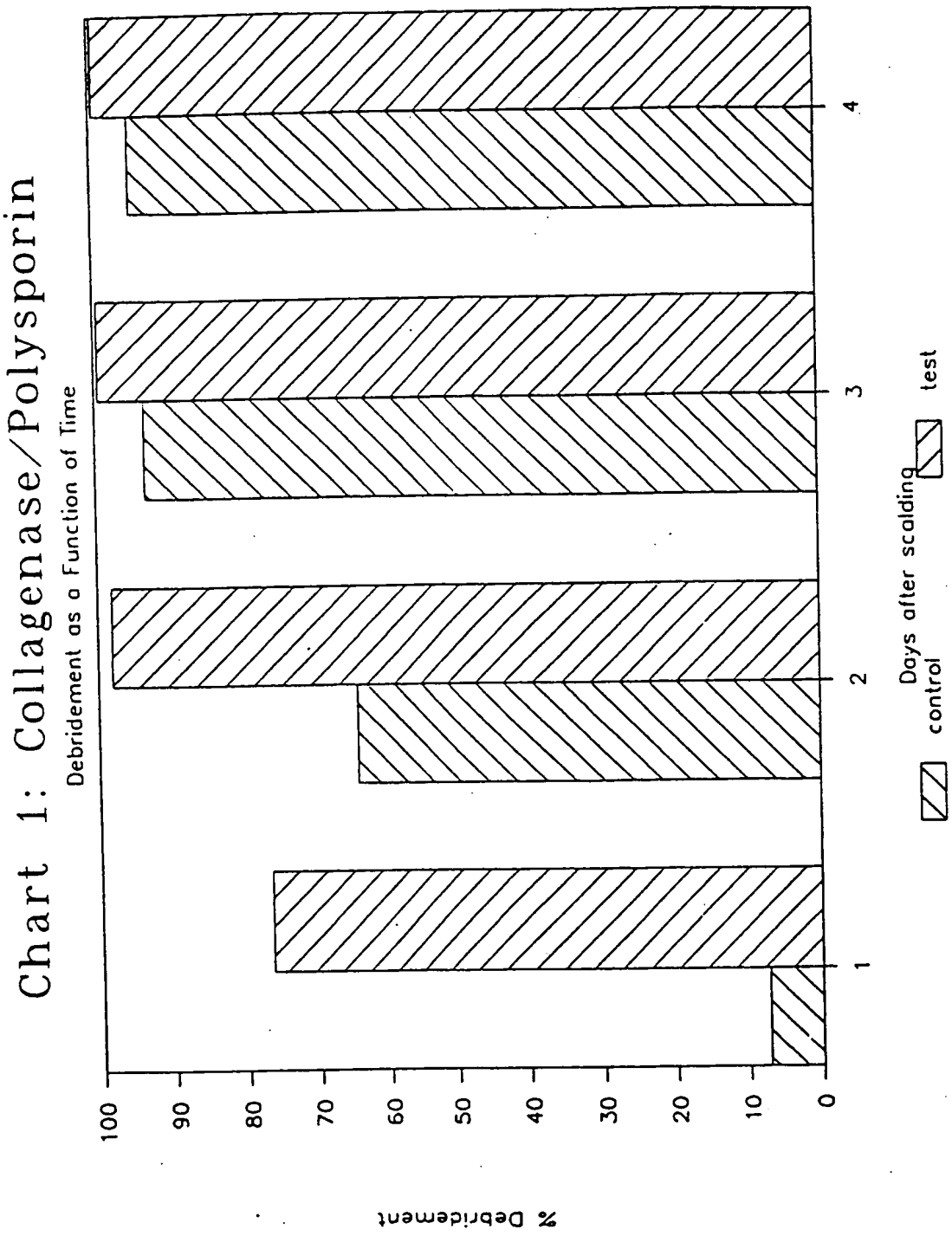
Chart 1: Collagenase/Polysporin
Debridement as a Function of Time
% Debridement
100
90
80
70
60
50
40
30
20
10
0
1
2
3
4
Days after scalding
control
test

Table 2: Percentage Debridement in Experiment Number 2 (Collagenase/Petrolatum)

Treatment	Side	<----- Days after scalding -----> 1	2	3	4
control	80R	0	15	25	70
control	81L	0	30	50	85
control	82R	0	0	20	65
control	83L	0	0	35	40
control	86L	10	25	85	98
control	87R	5	20	45	65
control	88L	5	50	90	98
control	89R	5	35	90	90
Mean		3	22	55	76
test	80L	25	50	98	98
test	81R	15	70	80	80
test	82R	20	65	90	98
test	83R	0	30	75	90
test	86R	20	30	75	98
test	87L	5	50	80	90
test	88R	25	65	85	90
test	89L	45	85	100	100
Mean		19	56	85	93
U		8.5*	6*	15.5	14.5

*significant at the 95% degree of confidence (two-tailed test)

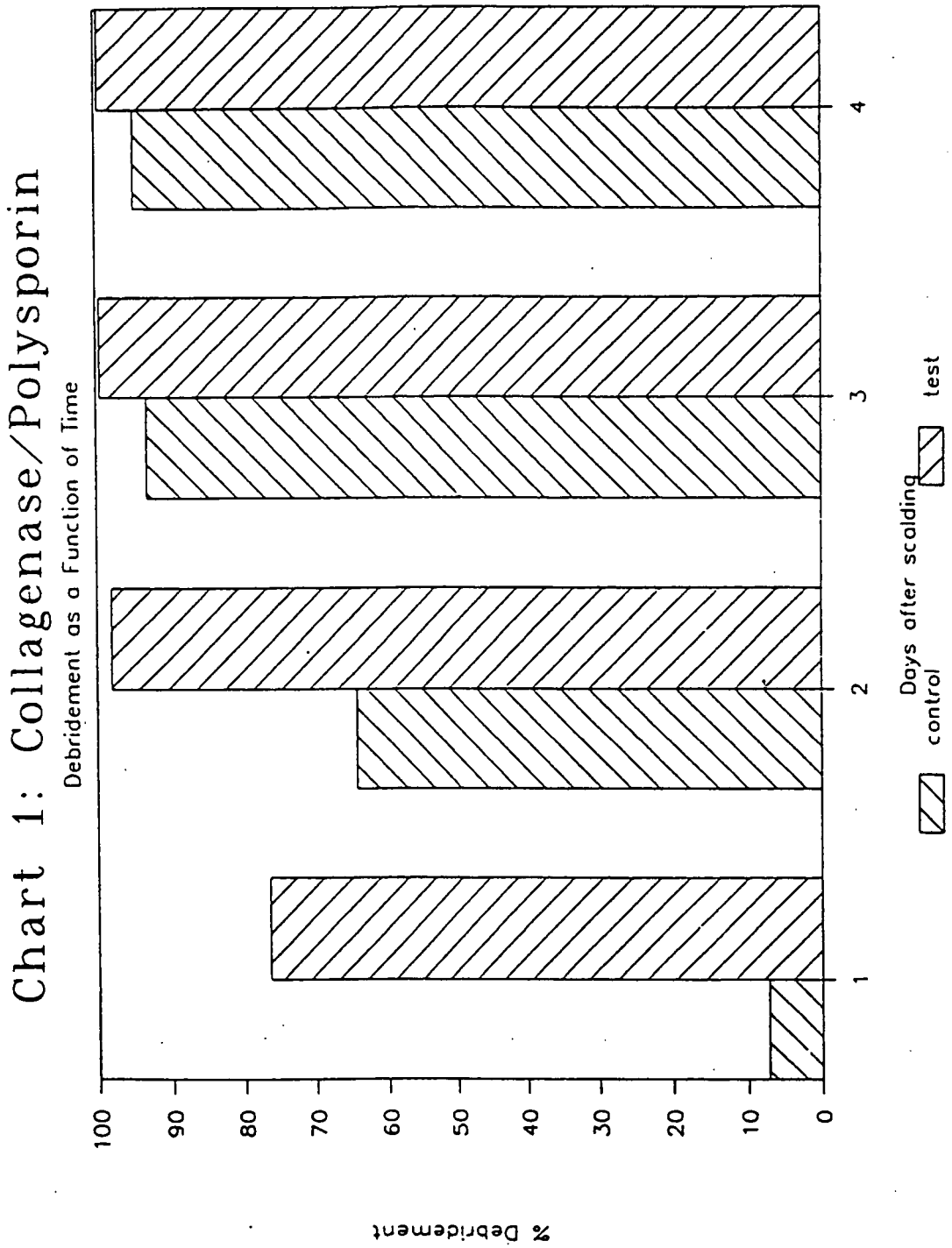
Chart 1: Collagenase/Polysporin
Debridement as a Function of Time
% Debridement
100
90
80
70
60
50
40
30
20
10
0
1
2
3
4
Days after scalding
control
test

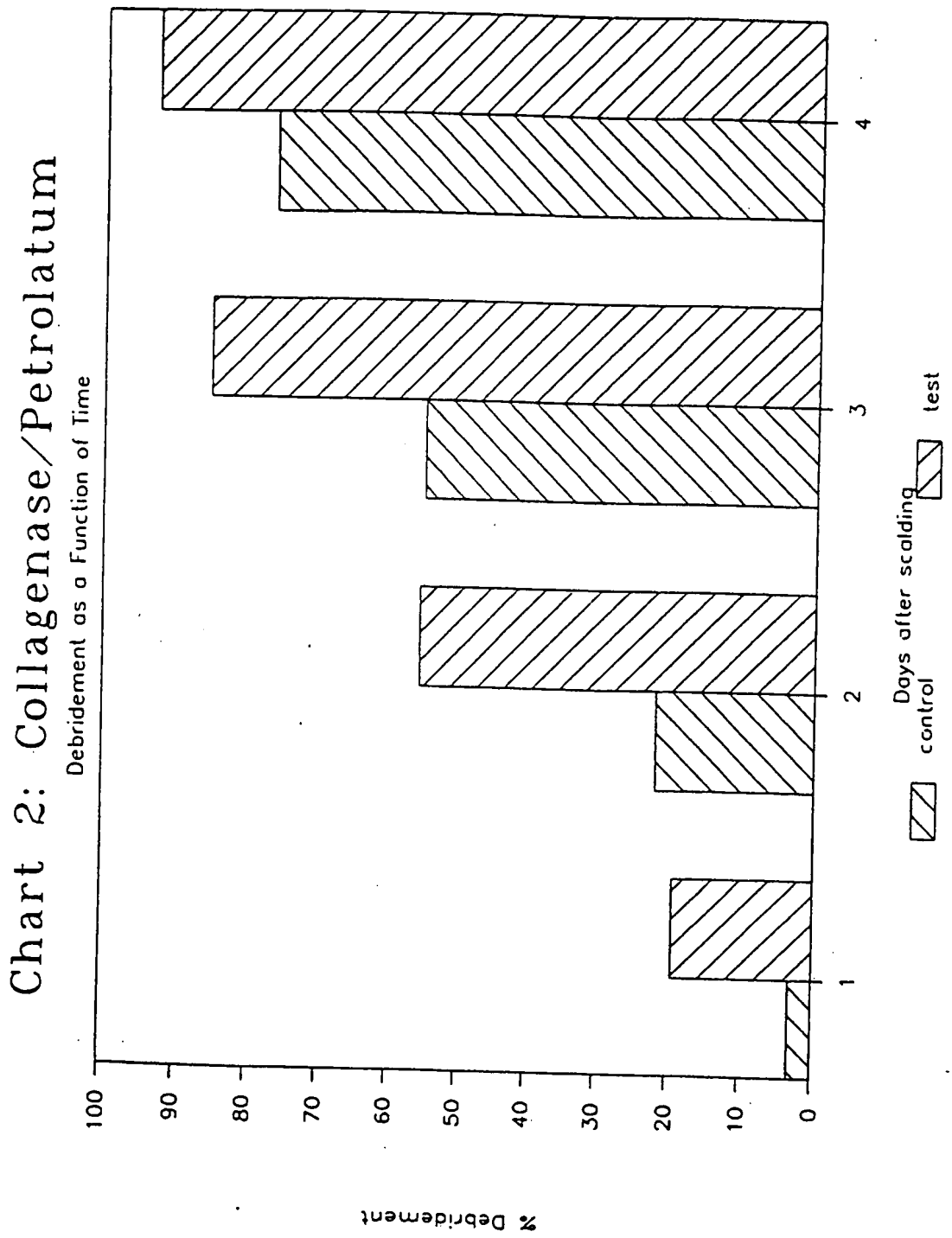
Chart 2: Collagenase/Petrolatum
Debridement as a Function of Time
% Debridement
100
90
80
70
60
50
40
30
20
10
0
1
2
3
4
Days after scalding
control
test

Table 1: Percentage Debridement in Experiment Number 1 (Collagenase/Polysporin®)

Treatment	Side	<----- Days after scalding -----> 1	2	3	4
control	57L	0	20	98	98
control	59R	0	75	95	95
control	60L	0	20	80	85
control	61L	0	75	95	95
control	62R	0	90	95	98
control	63R	50	90	95	98
control	64L	0	80	95	95
Mean		7	64	93	95
test	57R	85	99	99	100
test	58L	65	95	100	100
test	58R	75	98	100	100
test	59L	65	98	100	100
test	60R	50	100	100	100
test	61R	98	100	100	100
test	62L	80	95	98	98
test	63L	75	98	98	98
test	64R	95	100	100	100
Mean		76	98	99	100
U^*		0.5	0	1	3

*All U values are significant at the 99% degree of confidence (two-tailed test).

Table 3: Percentage Debridement in Experiment Number 3 (Collagenase/Lactose)

Treatment	Side	<----- Days after scalding -----> 1	2	3	4
control	91L	30	60	95	95
control	92R	0	15	75	95
control	94L	5	50	80	95
control	101L	0	20	75	90
control	102R	0	0	5	50
control	103L	0	0	20	85
control	113R	0	25	65	80
Mean		5	24	59	84
test	91R	75	85	98	98
test	92L	35	65	95	98
test	94R	35	85	98	98
test	101R	10	50	75	95
test	102L	15	60	80	98
test	103R	0	35	50	75
test	113L	5	70	85	98
Mean		25	64	83	94
U		8*	4*	11	7.5*

*significant at the 95% degree of confidence (two-tailed test)

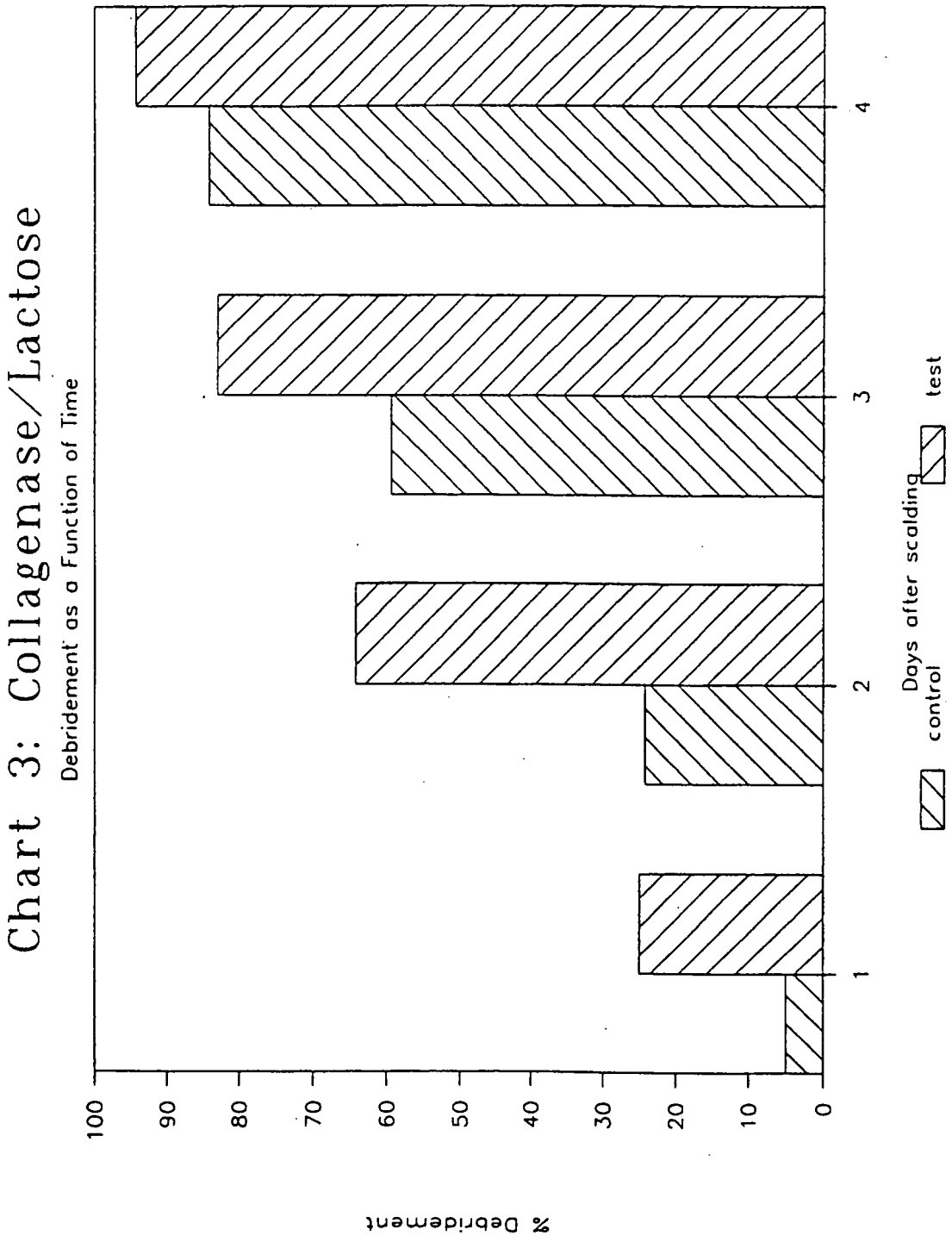
Chart 3: Collagenase/Lactose
Debridement as a Function of Time
% Debridement
100
90
80
70
60
50
40
30
20
10
0
1
2
3
4
Days after scalding
control
test